

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
27. Mai 2004 (27.05.2004)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2004/043426 A1

(51) Internationale Patentklassifikation⁷: **A61K 9/00**

(21) Internationales Aktenzeichen: PCT/EP2003/012272

(22) Internationales Anmeldedatum:
4. November 2003 (04.11.2003)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
102 52 726.1 13. November 2002 (13.11.2002) DE

(71) Anmelder (für alle Bestimmungsstaaten mit Ausnahme von US): **LTS LOHMANN THERAPIE-SYSTEME AG** [DE/DE]; Lohmannstrasse 2, 56626 Andernach (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (nur für US): **KRUMME, Markus** [DE/DE]; Feldkircher Strasse 46, 56567 Neuwied (DE).

(74) Anwalt: **FLACCUS, Rolf-Dieter**; Bussardweg 10, 50389 Wesseling (DE).

(81) Bestimmungsstaaten (national): AU, BR, CA, CN, HU, IL, IN, JP, KR, MX, NZ, PH, PL, RU, US, ZA.

(84) Bestimmungsstaaten (regional): europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Erklärungen gemäß Regel 4.17:

- hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii) für die folgenden Bestimmungsstaaten AU, BR, CA, CN, HU, IL, IN, JP, KR, MX, NZ, PH, PL, RU, ZA, europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)
- Erfindererklärung (Regel 4.17 Ziffer iv) nur für US

Veröffentlicht:

- mit internationalem Recherchenbericht
- vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: MULTI-LAYER TRANSMUCOSAL THERAPEUTIC SYSTEM

(54) Bezeichnung: MEHRSCHICHTIGES TRANSMUCOSALES THERAPEUTISCHES SYSTEM

(57) Abstract: The invention relates to a film-type therapeutic system (1) comprising at least two interconnected layers, for the transmucosal administration of active ingredients. Said system comprises a layer (2) which is mucoadhesive in an aqueous environment, and a single-layer or multi-layer rear layer (3). At least one of said layers contains active ingredients, and the cited mucoadhesive layer (2) is capable of swelling in aqueous media, but is insoluble or only slightly soluble.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft ein filmförmiges, mindestens zwei miteinander verbundene Schichten umfassendes therapeutisches System (1) zur transmucosalen Verabreichung von Wirkstoffen, welches eine in wässriger Umgebung mucoadhäsive Schicht (2) sowie eine ein- oder mehrschichtige Rückschicht (3) aufweist, wobei mindestens eine dieser Schichten wirkstoffhaltig ist, und wobei die genannte mucoadhäsive Schicht (2) in wässrigen Medien quellbar, jedoch unlöslich oder nur schwer löslich ist.

WO 2004/043426 A1

CLAIMS

1. Film-shaped therapeutic system (1) comprising at least two layers connected with each other, for transmucosal administration of active substances, which system (1) has a layer (2) which is mucoadhesive in aqueous environment and a mono-layered or multi-layered backing layer (3), at least one of said layers containing active substance, and the said mucoadhesive layer (2) being capable of swelling, but being insoluble, or only poorly soluble, in aqueous media.

2. Film-shaped therapeutic system according to claim 1, characterized in that the mucoadhesive layer (2) is made substantially of a polymer mixture which is film-forming, capable of swelling in aqueous media, but insoluble or only poorly soluble therein, and which comprises at least one hydrophile, mucoadhesive polymer which is embedded or dispersed in a polymer matrix.

3. Film-shaped therapeutic system according to claim 2, characterized in that the said mucoadhesive polymer(s) is/are selected from the group comprising carboxyl groups-carrying hydrophile adhesive polymers, polyacrylates and their salts, carboxymethyl cellulose and its salts, poly(methyl vinyl ether maleic anhydride) and its aqueous or alcoholic hydrolysates and salts.

4. Film-shaped therapeutic system according to claim 2 or 3, characterized in that the said polymer matrix is made substantially of one or more polymers selected from the group of the polyvinyl alcohols and polyacrylates.

5. Film-shaped therapeutic system according to any one of claims 2 to 4, characterized in that the polymer matrix of the mucoadhesive layer has been crosslinked by means of physical or chemical methods.

6. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that the backing layer (3) or - in the case of a multi-layered backing layer - the individual layers (3a, 3b) of the backing layer is/are manufactured on the basis of polyacrylates, preferably on the basis of neutralised polymethyl methacrylates.

7. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that the backing layer, or at least one of the individual layers of the backing layer, contains one or more auxiliary substances, preferably selected from the group of the plasticizers, penetration enhancers, solubilizers, dyes, pigments and matrix formers.

8. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that adjacent layers contain one or more identical or chemically allied base polymers, preferably from the group of the polyacrylates.

9. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that it is made up of 2 to 6 layers, preferably of 2 to 4 layers.

10. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that the backing layer, or the outer layer which is opposite to the mucoadhesive side, forms a boundary layer in which the permeation of water and the diffusion of active substance is reduced, relative to the other layer(s) of the system.

11. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that it is made up of at least three layers and comprises a mucoadhesive layer (2), at least one middle reservoir layer (3a) and an outer

backing layer (3b), with the latter layer forming a boundary layer in which the permeation of water and the diffusion of active substance is reduced, relative to the other layer(s) of the system.

12. Film-shaped therapeutic system according to claim 11 or 11, characterized in that the said boundary layer contains additives which reduce or block the diffusion of the active substance, particularly additives from the group of the pigments and the diffusion-retarding polymers.

13. Film-shaped therapeutic system according to any one of claims 10 to 12, characterized in that the reservoir layer(s) contain(s) one or more additives which increase the swelling capacity and the hydration of the reservoir matrix, said additives preferably being selected from the group of hydrophile, water-binding substances, with polyacohols and polymeric surfactants with an HLB value of ≥ 10 being particularly preferred.

14. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that the active substance(s) is/are present in dissolved, suspended or emulsified form.

15. Film-shaped therapeutic system according to any one of the preceding claims, characterized in that two or more layers contain the same active substance, preferably at different concentrations under formation of a concentration gradient.

16. Film-shaped therapeutic system according to claim 15, characterized in that the individual layers contain additives which bring about a modification of the solubility and the diffusion coefficient of the active substance in the respective layer.

PLACED IN 34 ANDT

17. Process for medicinal therapy or prophylaxis, wherein an active substance-containing film-shaped therapeutic system according to any one of the preceding claims is applied onto the oral mucosa and left there for a period of up to 24 h, preferably for a period of up to 6 h.

18. Process according to claim 17, characterized in that the active substance(s) is/are released with an initial burst dose and subsequently with a maintenance dose, the active substance delivery preferably taking place for a period of 0.5 h to 24 h.